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Case Report

A Case Report Series of Renal Cell Carcinoma Patients Treated with Nivolumab and Radiotherapy

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Abstract

Background: Many new targeted agents have represented an advance in management of patients with metastatic renal cell carcinoma (RCC), but the appropriate sequencing and combination of these agents in order to reach the best clinical outcomes is still a matter of debate.

Case Series: We present a case series of 3 patients with metastatic RCC. All patients underwent immunotherapy with Nivolumab and showed excellent survival outcomes and with a good toxicity profile. At least one case could represent a possible distant response after radiation therapy (abscopal effect) during immunotherapy

Conclusions: Immunotherapy represented an efficient and safe option for treatment of metastatic RCC patients, with excellent outcomes and a possible abscopal effect. Prospective data are needed.

Introduction

Renal Cell Carcinoma (RCC) is the most common tumor of the kidney, accounting for 90% of cases. RCC is characterized by large hystopathologic heterogeneity and is classified into three major histological subtypes: Clear-cell RCC (70% to 85% of cases), Papillary RCC (7% to 15%) and Chromophobe RCC (5% to 10%). Twenty to thirty percent of patients present with metastatic disease at diagnosis, and an additional 30% of patients will eventually develop distant metastases after local treatment [1].

Guidelines for first line treatment of metastatic disease include various options. Tyrosine kinase inhibitors (e.g. Sunitinib, Pazopanib, Axitinib or Sorafenib), anti-VEGF receptor agents (Bevacizumab) or mTOR inhibitors (Temsirolimus) are all approved in this setting [2]. Nevertheless, progression after first-line systemic agent is still associated with poor overall survival.

Nivolumab is a fully humanized monoclonal IgG-4 antibody that blocks the interactions of programmed death 1 (PD-1) checkpoint inhibitor that would result in inhibition of immune response. Recently, Nivolumab showed survival advantage over Everolimus in a randomized phase III trial that enrolled patients with metastatic RCC who progressed after one or two previous regimens of antiangiogenic therapy [3].

Moreover, Nivolumab showed promising results in health-related Quality of life [4], and a subset analysis of checkmate 025 showed an extended benefit of anti PD-1 treatment beyond progression [5]. Overall, these studies promote the use of immune therapy for second-line treatment of metastatic RCC. Interestingly, data from literature suggested promising interactions between radiation treatment (especially Stereotactic Body Radiation Treatment, SBRT) and immune therapy. These interactions could represent a radical change for the role of radiotherapy in the metastatic patient, as an adjuvant for immunotherapy [6]. Still, proper timing of radio-immunotherapy combination and clinical indications of this strategy remain unknown [7].

In this study a series of three cases of patients affected by metastatic RCC and treated with nivolumab is presented; for all of them, excellent results in terms of survival have been observed. Data from their clinical records are described, representing different treatment options available in a real-life scenario after at least one systemic therapy. The purpose of the current manuscript is to offer our experience in the management in these peculiar patients, in whom the integration between radiotherapy and anti

PD-1 treatment may further improve the outcomes.

Case Series

Case Report No-1

The first patient is a 47 years old man affected by RCC who underwent a left nephrectomy in 2014. In June 2015, a follow up CT scan showed several new metastatic lung nodules, and systemic therapy with Sunitinib (50 mg PO daily for 4 weeks followed by 2 weeks drug-free interval) was started.

After three months of treatment, patient referred worsening dyspnea and a CT scan showed pulmonary progression with pleural effusion. After three thoracentesis and a thoracoscopic talcage, reported Karnofski performance status was 80, and in December 2015 patient was included in a compassionate use program with Nivolumab 3 mg/kg q14, and started treatment.

Nivolumab was administered for a total of 31 cycle, until June 2017; during the treatment, evaluation CT scans were performed every 3 months, showing stable disease. The only adverse event reported occurred between the 23th and 24th cycle of Nivolumab, when P.G. underwent a brain MRI and a CT angiogram for the onset of headache and diplopia, showing cerebral hemorrhage in the context of a hemorrhagic cyst. Patient underwent surgical removal of the lesion, histological result was negative for RCC.

Case Report No-2

The second patient is a 53 years old man affected by RCC who underwent a surgical left nephrectomy in the year 2000. Subsequent radiological follow up evaluation was negative until 2007, when a CT scan showed the appearance of a single pulmonary lesion. Patient underwent surgical resection, confirming its secondary nature, followed by observation with CT scan every three months. In the 2010 the patient underwent a treatment based on Sutent in another center.

In November 2013, a CT scan showed two new pulmonary lesions in the right lung, of 21 and 16 mm in the greatest dimension, situated below the 11th costovertebral joint and at hilar level. Stereotactic radiotherapy with a total dose of 30 Gy in 3 fractions was administered targeting both lesions. The treatment plan was elaborated using a 4D-CT scan, and a cone-beam CT was performed before each fraction and registered to the planning CT to provide image guidance and correct setup error.

In April 2014 a CT scan revealed a 30 mm new pulmonary lesion at the right inferior lobe, and the patient underwent a new stereotactic treatment for a total dose of 35 Gy in 5 fractions. A new symptomatic lesion on D11 vertebral body was detected by CT scan at the end of 2014. SBRT was administered with 25 Gy in 5 fractions, followed by subcutaneous Denosumab 120 mg q 28, since the previous nephrectomy and the subsequent impaired renal function.

Radiological assessment showed stable disease until July 2015, when multiple pulmonary and new bone lesions were evidenced and systemic therapy with Everolimus (10 mg daily) was started. The main reported toxicity during Everolimus treatment was a G3 mucositis (according to NCTCAE scale [8]) that completely regressed after medical therapy with oral corticosteroids.

In October 2015 a further skeletal progression due to the appearance of a paravertebral lesion at D11 level was evidenced by a CT scan. Thus, C.M started systemic treatment with Sorafenib 800 mg daily. Moreover, SBRT for a DTF of 12 Gy ina unique fraction (IDL 70%) was administered using Cyberknife in December, 2015. Sorafenib was interrupted for seven days before SBRT, and resumed just after end of treatment.

Disease remained stable until February of 2016, when new pulmonary progression occurred. Sorafenib therapy was interrupted and the patient was enrolled in a compassionate use program with Nivolumab 3mg/kg q 14. After seven cycles of Nivolumab, a CT scan performed in July 2016 showed partial response on all sites of disease. An encephalic progression (a new 59x41 mm lesion situated in the right temporal lobe) was evidenced in October 2016, after XV cycles of Nivolumab, and, after the patient underwent a surgical excision of the lesion. Nivolumab was continued one month after the surgery until the February of the 2017 when a new encephalic progression (a new lesion of 2.5cm in the left temporal site) was discovered during the follow up.

This new lesion was treated with SBRT for a DTF of 18 Gy in a unique fraction with the GK system and after one month a MRI was performed showing stability of the disease. Disease remained stable until the last CT and MR scan, performed on the April of the 2017, and patient did not report any new symptoms.

Case Report No-3

The third case is a 75 years old man affected by RCC, on the right kidney, surgically removed in August 2013. In February 2015, a follow-up CT scan showed the appearance of 2 pulmonary lesions and first-line treatment with Pazopanib 800 mg daily was started. After nine cycles, a CT scan performed in January 2016 showed lung progression, and second-line treatment with Nivolumab 3 mg/kg was started for compassionate use. The Patient underwent a total of 25 cycles of Nivolumab, and disease assessment was performed by periodic CT scan every 3 months, evaluated according to iRECIST criteria [9]

In April 2017, a 6 mm encephalic lesion was found on re-evaluation CT scan. A following MR confirmed the site and the dimension of the lesion. In consideration of the complete absence of symptoms and the overall stability of disease, it was decided to pursue a wait-and-see approach, with a re-evaluation MRI performed after two months that showed a stability of the disease.

Discussion

Overall, these three cases showed excellent outcomes in patients treated with immunotherapy after progression under one or more previous line of systemic therapy administered in metastatic setting. Considering that the reported median first-line time to progression is about 9 months, with a second-line time to progression ranging between 5 and 10 months [10], the results observed in the cases reported are outstanding; Moreover, patients had an acceptable safety and tolerability profile during the treatment. The second case report illustrated an integrated approach between systemic and local treatment, applied in a real clinical practice scenario.

It is difficult to quantify the benefit of using a local treatment in patients with metastatic RCC, but prospective data about the feasibility and efficacy of this kind of integrated treatment are needed. Interactions between radiotherapy and immune therapy are of great interest in this subset of long surviving, oligoprogressive patients, treated with immune therapy. Pre-clinical data suggested a synergistic effect of these treatments, based on the potential immune stimulating properties of RT, especially in extremely hypofractionated treatments [11-17].

One of the most intriguing debating matters is the effect of local SBRT on control of distant sites of disease (the so-called "Abscopal effect" [18]), especially in combination with immunotherapy [19]. In one of the cases presented, partial response of disease to Nivolumab treatment after SBRT on a site of encefalic progression was reported. In this case, potential effect of SBRT on immune activation against tumor antigens expressed on distant sites of disease could be hypothesized. However, no conclusion can be drawn about this aspect, but this case report series shows how availability of systemic treatments and development of new radio therapy techniques may change current clinical practice. The third case presented could be considered paradigmatic: if the patient will become symptomatic or the lesion become beiger, local treatment on the encephalic lesion could allow to maintain the same systemic scheme of treatment, but the treatment could be postponed in case of disease stability.

Conclusions

Integration between anti PD-1 agents and new radiotherapy technique could be of mainstay importance for management of metastatic RCC. Prospective data are needed to develop new therapeutic strategies and explore the correct timing of treatment timing.

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